UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

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ANTIVIRAL DRUGS ADVISORY COMMITTEE

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MEETING

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WEDNESDAY, JANUARY 10, 2001

0 a.m., in Versailles I, II, and III, Bethesda Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland, Roy M. Gulick, M.D., M.P.H., Acting Chairman, presiding.

PRESENT:

ROY M. GULICK, M.D., M.P.H., Acting Chairman

WILLIAM BLACKWELDER, Ph.D., Consultant (Voting)

COURTNEY V. FLETCHER, Pharm.D., Member

JOHN R. GRAYBILL, M.D., Guest

RANA A. HAJJEH, M.D., Consultant (Voting)

PRINCY N. KUMAR, M.D., Member

PRESENT: (CONT.)

WM. CHRISTOPHER MATHEWS, M.D., M.S.P.H., Member

JOHN R. PERFECT, M.D., Guest

JONATHAN M. SCHAPIRO, M.D., Guest

SHARILYN K. STANLEY, M.D., Member

DAVID STEVENS, M.D., Guest

BRIAN WONG, M.D., Member

TARA P. TURNER, Pharm. D., Executive Secretary

C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

(8:35 a.m.)

ACTING CHAIRMAN GULICK: Good morning. We'll begin.

I'm Trip Gulick from Cornell, acting as chair today of the Committee.

First up I would like to go around the committee and have everyone introduce themselves and state their affiliations, starting with Dr. Schapiro.

DR. SCHAPIRO: I'm Dr. Jonathan Schapiro from Tel Aviv and Stanford University.

DR. STEVENS: David Stevens, Stanford.

DR. GRAYBILL: Dick Graybill, not from Stanford, from South Texas, San Antonio, on the border with Mexico.

DR. PERFECT: John Perfect, Duke University.

DR. FLETCHER: Courtney Fletcher from the University of Minnesota.

DR. TURNER: Tara Turner, Executive Secretary for the Committee.

DR. MATHEWS: Chris Mathews, University of California, San Diego.

DR. HAJJEH: Rana Hajjeh, Centers for Disease Control.

DR. STANLEY: Sharilyn Stanley, Texas Department of Health, just a little north of San Antonio and Austin, and we happily ceded you a President recently.

DR. WONG: Brian Wong from the West Haven VA and Yale University.

DR. KUMAR: Princy Kumar from Georgetown University.

DR. BLACKWELDER: I'm Bill Blackwelder, statistical consultant.

DR. DIXON: Cheryl Dixon, FDA.

DR. NAVARRO: Eileen Navarro, FDA.

DR. GOLDBERGER: Mark Goldberger from the FDA.

DR. MURPHY: Dianne Murphy, Office Director, ODE IV, FDA.

ACTING CHAIRMAN GULICK: Thank you very much.

It seems like we have a Texas leaning for some reason this morning.

No, it's not a political comment. Thank you.

(Laughter.)

ACTING CHAIRMAN GULICK: Tara Turner will now read the conflict of interest statement.

DR. TURNER: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions.

In accordance with 18 USC 208(b), full waivers have been granted to Drs. Brian Wong, Courtney Fletcher, and Roger Pomerantz. Copies of these waiver statements may be obtained by submitting a written request to FDA's Freedom of Information Office located in Room 12A30 of the Parklawn Building.

In addition, we would like to disclose for the record that Drs. Roger Pomerantz and Princy Kumar have interests which do not constitute financial interests within the meaning of 18 USC 208(a), but which could create the appearance of a conflict. The agency has determined, notwithstanding these interests, that the interest of the government in

their participation outweighs the concern that the integrity of the agency's programs and operations may be questioned.

Therefore, Drs. Roger Pomerantz and Princy Kumar may participate in today's discussion of Cancidas.

With respect to FDA's invited guests, there are reported interests which we believe should be made public to allow the participants to objectively evaluate their comments..

Dr. David Stevens would like to disclose that he and his spouse own stock in Merck. His employer, Stanford University, has received research grants from Merck, Bristol-Myers, Fujisawa, Gilead Sciences, Sequus, Alza, the Liposome Company, Janssen, Aronex, and Ortho Biotech.

Currently, he is consulting for Gilead Sciences and has in the past consulted for Merck, Sequus, Alza, Janssen, Aronex, and Ortho Biotech.

Additionally, he has received speaker fees from Merck, Gilead Sciences, Sequus, Alza, the Liposome Company, Janssen, Ortho Biotech, Abbott, and Nextar.

Dr. John Perfect would like to disclose that he has consulted and lectured for Merck on

antifungals. Aronex, Liposome Company, and Merck have been sponsors of his research.

He also received honoraria from Merck, Fujisawa, and the Liposome Company.

Dr. Perfect has served as a scientific advisor to Merck, Gilead Sciences, the Liposome Company, Janssen, Ortho Biotech, and Bristol-Myers Squibb.

Additionally, his employer, Duke University, has considered a study of Merck's MK0991 for aspergillus salvage therapy, but the study was never activated.

Dr. John Graybill would like to disclose that he has served as a consultant to Merck, Ortho Biotech, Versicor, Microside, and Schering. His employer, the University of Texas Health Science Center, is receiving research funding from NIH, NIAID, and Schering-Plough.

Pending research funding is anticipated from Versicor, Incorporated, Merck, NIH, NIAID, and Fujisawa.

Merck has also provided past research funding.

Further, Dr. Graybill is named as co-investigator for a Merck aspergillosis protocol.

However, he has not been engaged in any care of any patient's treatment with caspofungin for aspergillosis directly or indirectly.

Dr. Graybill's clinical involvement with caspofungin has been entirely with Candida.

Additionally, Dr. Graybill has also received speaker fees from Merck, Ortho Biotech, the Liposome Company, and Pfizer.

Dr. Jonathan Schapiro would like to disclose that he formerly refused an offer from Merck to serve as a consultant. Currently he is negotiating a contract with Roche to study Fortovase.

He has also received honoraria from Roche for his past lectures on HIV resistance.

In addition, Dr. Schapiro has served as a scientific advisor to Roche and Agouron. His employer, UCLA, has a Web site on HIV resistance which had received support from Roche in the past. Other firms may provide support in 2001.

Lastly, Dr. William Blackwelder would like to disclose that in 1998, he served as a consultant to Merck Research Laboratories on MK0991.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest,

the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you.

I have an announcement. There's a car that's blocking a hotel guest. It's a white Mercedes with Virginia tags BDP-1. Please move your car immediately.

Thank you.

ACTING CHAIRMAN GULICK: Okay. Thank you.

I'd like to turn this over to Mark Goldberger for some introductory remarks from the FDA.

DR. GOLDBERGER: Thank you.

We'd like to obviously extend our welcome to Advisory Committee members, invited guests, the sponsor, as well as everyone in the audience.

Today we're here to talk about Merck's application for caspofungin for treatment of serious infections due to aspergillus that are refractory or intolerant to standard therapy.

I think everyone is aware of how

challenging an issue this is. When I used to practice infectious disease some years ago, it was very challenging, and despite all of the progress we have made in many areas and in microbial therapy, it remains today essentially equally challenging.

We would like to start off by thanking Merck for the enormous efforts they've made in putting this application and this program together. Not only is this a difficult infection to treat, but it's actually a fairly difficult infection to study as well.

It's always very exciting to be able to talk about a new class of antimicrobial as we are today. This is the first drug of this class to come forward for an approval. Obviously this is exciting. It's always challenging since the amount of previous information we have on the class is less than when we're dealing with drugs for which similar drugs have already been approved.

We will be obviously asking you to look at the overall data that exists to comment on the safety and efficacy. We will also be asking you, in particular, to look at the control group that Merck has chosen to use, the historical control, which is permitted under the FDA regulations as one way to do

an adequate and well controlled study, but always presents unusual challenges in terms of looking at the comparability of historical controls to the active treatment group.

We believe Merck has done a fine job in this, but nonetheless not unsurprisingly, there are still unresolved issues that will need some discussion.

The other thing we would like you to do at today's meeting is to keep in mind that this is an area where not only is it challenging to treat, but it has begun to attract a great deal of development of new products.

And we have asked a couple of questions that deal with the kind of information that one would like to have to modify indications in this area and also, in general, issues related to study design, and we would really like, you know, your opinions about this because it will be extremely helpful in terms of the advice that we're able to provide to other sponsors as they put together their development programs.

Thank you, and we're looking forward to an interesting meeting.

ACTING CHAIRMAN GULICK: Thanks very much.

The first presentation will be Dr. John Perfect from Duke University, speaking about the treatment of aspergillosis.

DR. PERFECT: Well, thank you, and I appreciate Dr. Navarro's opportunity for me to come to talk today.

She said that I could talk about anything I wanted as far as treatment of aspergillosis, and so I decided -- and she said initially 20 minutes, and then she said 30 minutes. So hopefully I'll stop in 30 minutes. But what I'd like to do is go over some issues to set the stage for the discussion on the specific drug caspofungin, but to talk about aspergillus, where we're at, what's happening on the wards, what's happening in the studies, what do I think the advances are going to be.

And since she gave me free rein, this is what you're going to hear.

Now, some of you may have handouts. She asked that I give handouts, and I said 30 or 35 would be enough. So it looks like there's a little more than 30 or 35 here, but if anybody wants handouts of these things, please let me know later. They're just copies of the slides that you're going to see.

I want to talk about the treatment of

aspergillosis, and I think what you're going to see is many of the difficulties of this disease process, not only the underlying diseases, but the difficulty in determining outcomes.

And I'm going to go through a series of events trying to analyze that.

This is the beast; this is the organism, septated hyphae in tissue, the prominent mold infection that we see today, although we are seeing a series of other molds, including Fusariums and P. bullae (phonetic) infections. Aspergillus is the major player.

It's tough. It's a tough infection.

Can the lights go down a little bit?

It is a tough infection. I put it up here as one of the tougher infections I've seen. Actually this is one of the easier infections that I have seen. There is an unfortunate gentleman who had a problem with a lawn mower, and when we took his cast off, you could see the aspergillus growing here on the tissue.

That's easy to treat. All you do is wash it off. However, these are the tough infections. These are the tough infections of the neutropenic patients where you see a category (phonetic) lesion here with a fungus ball, or this particular patient

that is neutropenic, and I apologize for the lights here to actually see this, but let me describe it.

This is a neutropenic patient. Actually there is an eschar right here, and actually the aspergillus is burrowing its way through the palate and actually burrowed its way into the brain over time.

These are very, very tough infections to treat. The outcomes in many of these cases are severely abrogated.

Now, let's talk about what's happened with aspergillus as far as outcomes. I'm going to use two studies. One, David Denning's study from 1998 on hematology/oncology patients. I think this is important to identify, 1998. Three-month survival of patients with aspergillus, three-month survival, pretty good endpoint, final endpoint, 36 percent survival.

Now, that takes into account all of the underlying disease, takes in the infection, takes in the whole picture. But, again, as you can see here, 36 percent of patients are alive at the end of three months.

These are all patients, 1995, from a study that we have done in the Mycoses Study Group. They're

all patients, both hem.-onc., non-hem.-onc., and it's 25 centers.

And if you look at what the survival rate was, 1995, three-month survival rate, 38 percent. Very common statistics, that about a third of the patients will survive three months, and no matter what endpoint you say, that is as solid as you can get.

Now, what we did was to break this down a little bit, and these are tough issues to break down, particularly death due to aspergillus. What is death due to aspergillus, and how do you define that?

But with experts in the field looking at the cases, looking at the cases retrospectively from the charts, in this study of all patients here that survived only a 38 percent, death due to aspergillus decided by the investigators ran in the range of about 40 percent, with the underlying disease and other causes coming in.

So, again, the aspergillus itself, the infection itself, including the underlying disease has a major impact on mortality, and these are fairly solid statistics that I think are not going to change in the immediate future.

So that's the background. That's the seriousness. That's the life threateningness

(phonetic) of this particular infection.

Now, I thought I'd give the practice guidelines. This was done by a lot of experts, including those in the audience, that was published this last year in CID, practice guidelines for the treatment of aspergillosis.

And both for invasive aspergillosis, aspergilloma, allergic bronchopulmonary aspergillosis, and there's a certain grading system, As being well established, Bs being less, Cs and on down. And whether those studies have actually been done, were they good, randomized, placebo controlled studies at one, less studies at a two, maybe no studies done actually at three, but that's the standard of practice. So as you go down, they rank these.

And you can see here for invasive aspergillosis this was the recommendations with areas of having some decent studies, but a lot of this still being used more on what the standard of care is in the community.

And I have to laugh at this a little bit. Nothing wrong with it, but things evolve very fast in this area, and I'm very impressed that this final recommendation for guidelines as amphotericin B deoxycholate at a dose of one to 1.5 milligrams per

kilogram per day.

Now, there may be hospitals, and maybe there's a lot of hospitals out there treating aspergillus infections with one to one and a half milligrams of amphotericin B, but in this day and age in our hospital with the underlying diseases, the various types of drug interactions that we have, I can't think of a patient in the last two years that we've actually treated with this high a dose of amphotericin B for invasive aspergillus. It just simply we might start them out on that; we just couldn't get through the course.

So this is the only recommendation from these practice guidelines that we have of any type of dosing structure for the actual treatment of invasive aspergillus.

I'm also very interested in surgery here, which didn't have a high ranking, for aspergilloma. I recently reviewed 25 hospitals and aspergillomas, which there were about 50 to 60 cases of aspergilloma. How many patients were actually treated with surgery? One out of about 60, about two percent. Even though this is the recommendation, many of these patients simply don't or can't tolerate surgery.

And, finally, allergic bronchopulmonary

aspergillosis, which actually I put the highest ranking here because there has been a randomized, placebo controlled study in the impact of itraconazole on allergic bronchopulmonary aspergillosis, and as you can see here, I think it gets probably the highest ranking of any of the types of practice guidelines that we have today.

So that's the background. That's the background of what the doses are. That's the background of the experience, and it's still an evolving area, that in fact even the guidelines aren't up to what's happening in the clinics today.

Okay. Now, this is a tough infection, bad mortality, still not great drugs. I thought I would take a viewpoint of strategies to overcome drug resistance and take each one of these from accurate, rapid diagnosis, down to the new drugs, which is something we're here today to talk about, and give some insights or at least some opinions of how aspergillus fits into these strategies that we have to come up with to overcome drug resistance.

But, first, a comment on accurate and rapid diagnosis. We've improved. We've improved with cryptococcus and histo., but in aspergillus, if I focus on this, the glactomannan and glucan tests for

those are still evolving, and I am not terribly impressed that even a year or two, even if FDA approval does occur with some of these glactomannan tests, that we will know exactly how to use them.

And I'm not yet impressed that PCR at this stage is going to be in our immediate repertoire of strategies in management of these patients.

However, rapid diagnosis is important. When the burden of organisms is lower, the chance of success is going to be greater. So even though I'm a little depressed at this stage to say that this is going to be an immediately part of the future, I think it is the potential part of the future, particularly in randomized studies, prospective studies in high risk patients to detect the infections at a lower burden of organism.

Now, immunomodulation in mycoses. We have well defined studies, cytokine studies, a basic part of basic science today, very, very good studies. Theoretically this is an important issue. Theoretically the immune system is very important here. Theoretically these immune compromised patients should be helped by immune modulation.

However, I'm not convinced yet that we clinically have optimized how to use the new

modulation, and I'm not enthusiastic that's going to happen overnight. I think it will take potentially years.

And I think I'd just like to give a couple of examples of that because we have now had growth factors for a long time. Do they have an impact on aspergillus? Well, maybe, but actually if you look at the David Denning and group out of Europe, the EROTC multi-center prospective study of invasive aspergillosis in hematological patients, diagnosis and therapeutic outcome, 130 cases, 20 hospitals, eight countries. The use of growth factors had no influence on the outcome in aspergillus.

Now, recently I was at a meeting in actually Barcelona, and Dr. Todeschini there presented something that I've actually seen. Sometimes you think growth factors and immunomodulation may help, but if you don't know exactly how to use it, maybe it sometimes can actually hurt, and I've seen this myself.

And this is an example of what they had using growth factors in aspergillus during neutropenia. When white cells went from zero to 4,500 rapidly, over less than five days, their death rate was 50 percent.

When they had a slower rate, which again we want to get the white cells back where we will never ever treat these infections, when they got them back over a slower time, they actually had only a death rate of about 17 percent.

Now, these are not statistics that are going to go up to any P values or whether it's actually real or not, but myself, I've seen patients where we've pushed to get the white cells back very fast. They come back very rapidly, and they degranulate in the tissue, in the lung, and the next thing we know, we have ARDS, and the patient dies very, very fast.

So I want to make a caution that I'm not convinced yet we have great study for immunomodulation, and sometimes playing with immunomodulation may make the infection worse rather than better.

Now, dosing is the thing that I think that we still need more potential work on. I don't think we've actually optimized triazole pharmacokinetics, and even worse than that, i don't think we really yet know the proper daily dose for some of the lipid products of amphotericin B in aspergillus or other types of infection.

I'm not sure yet whether we should explore the idea of administering these drugs at different sites that might help, and I thought I'd give a couple examples of the question of daily dose of lipid products of amphotericin B, and I'll give an issue that we ended up with, which is looking at putting the drug at certain sites of infection, in other words, optimizing our dosing.

Now, this is AmBisome. This is a study in aspergillus that Dr. David Ellis and group in the EROTC, may be well known to many of you in the audience. It was actually trying to make some attempt in dosing and the importance of dosing in aspergillus, and this was a study, a moderately small amount of patients, with a one milligram versus four milligram dosing schedule, and this is complete or partial response.

And as you can see here at this stage, complete and partial response, 64 percent versus 48 percent, suggesting that one milligram may be as good or potentially better than four milligrams per kilogram.

Surely that type of study is in conflict, I think, with any of the animal models that have been done, and I think our own feeling on this is that more

with the lipid products or more with amphotericin B is probably better.

You go back to that study and you break it down and you look at definitions, and definitions are hard, difficult issues in this disease process, and I think you've got to be very careful of those studies and what they call invasive disease and what they don't.

If you actually broke this study down into definite, well documented disease, you actually reduce the numbers here, and actually, if anything, the higher dose was a little bit better than the lower dose.

The important point of this is you've got to be very, very careful of the patient population and the definitions that you put into that population.

I put down here some other studies, and I put it down to even five milligrams, and again, a fairly small study our of the British Journal of Haematology, where it actually suggested a complete response of 77 percent or so, and again, I would like to caution you on what you mean by response and the definition of that, and that may change.

Some people use the Mycosis Study Group criteria. Some use their own criteria, and that may

change what that final figure and outcome is.

And then, of course, another study with a little higher, with about a 52 percent success rate, and they compared this, at least a comparative study -- Leenders did -- to amphotericin B, and you'll hear more about this on the historical controls in a little bit, suggesting that actually the higher dose of five milligrams per kilogram might be better than the standard dose of amphotericin B, at least in that study.

I want to come back and remember these percents, and I don't want to say they're fixed, but you're going to see the kind of things you're going to have to deal with in the final outcome of these type of patients and complete and partial response. And remember the patient population and the criteria for that success.

Now, with aerosolized drug in our own experience, we had problems in lung transplants as we started with a lot of infections. We decided for a lot of reasons that we should actually study the organ itself and protect that organ from an infection, particularly with aspergillus, et cetera.

So we came up with a protocol, aerosolized ABLC for fungal prophylaxis in lung transplants. We

had over 100 patients we went to the FDA now on with a reduced toxicity less than three percent, and this is pre a lot of biopsies, a lot of spirometry, and stuff like that, really very easy stuff to give, very safe, and probably fairly cheap.

Over that time, 100 patients, no pulmonary infections. An occasional fungemia we will get because this is not a systemic administration. This is a local protection, and this was the doses that we used.

We are now in the range of a randomized study comparing whether do you need the lipid product, which may be aerosolized better, or can amphotericin B actually work in this, protecting this lung in a prophylaxis setting.

The other day we just had a meeting on this, and our pulmonary people are bored with the study. We're up over 50-some patients now, and they just don't see anything happening here. They actually want to break it, and I said, "Guys, we should at least go to 100 patients to study this."

But the point is you need to look at areas of both prophylaxis prevention and also administration of these drugs and optimize the pharmacokinetic dynamics that can occur.

Now, the point I want to make on prophylaxis is I'm not going to spend a lot of time on it, but I can't go by it to say that I think the primary success that will occur in the next ten to 15 years in aspergillus will be strategies to prevent these infections rather than actually treat them. An ounce of prevention is worth a pound of cure.

These infections when a high burden of organisms, immune suppressed patients are difficult, at best, to cure, and if we identify patients, get kind of strategies to prevent these infections, we're going to be better off.

I use the ten percent rule within the hospitals. I'm not sure statistically somebody will beat me to death, but I'm not convinced that we will ever get to zero on these type of patients, and even some of the good studies of fluconazole and Candida infection, there was two to four percent background range.

So in any institution, you'd better look at your population, identify your population, and have at least probably a ten percent incidence of fungal infections to make any impact on prophylaxis within your own institution.

And with aspergillus, I'm not convinced

yet we really have good, excellent prophylaxis studies to prevent aspergillus. I told you about ours in lung transplants. So it's been fairly successful, but a randomized study to show impact on aspergillus infections in these patients with prophylaxis is still awaiting further studies.

I want to bring up the point of empiric therapy. Some of the best, best studies that we have today undoubtedly have been the empiric, febrile neutropenic studies for prevention or early treatment of fungal infections.

This is a study Tom Walsh did in the New England Journal, well known to many of you here, a large study, randomized, and you can see here in aspergillus, the AmBisome group, these are breakthrough fungal infections which do have an impact in the final outcome of these patients, although there was no difference in the final outcome between the two groups. Within the breakthrough fungal infections there was. It surely is telling us something about the biology of the treatment here.

And if you look at aspergillus, the AmBisome had five and the amphotericin B had 11, suggesting that there might be some difference in the early treatments or the early management of

aspergillus.

Now, you keep this in mind, and a most recent study of a very similar, large study, febrile neutropenia patients with AmBisome versus voriconazole that was at the ICAAC meetings in 2000, and if you break this down, again, a very similar design. No difference in outcome of these patients. Final outcome, no different.

But if you look at breakthrough fungal infections, which does have an impact on the final outcome of these patients, surely no one want so to have an aspergillus infection. No one wants to deal with it.

You can see here the amount of aspergillus infections in the Voriconazole group were four and the AmBisome group were 13. So is there something, as we do these strategies, of improving the incidence of aspergillus infections in these high risk patients?

It would be suggested from a very large study that we are making some impact.

Now, what about surgery? I can't spend a lot of time on surgery. I think it is an impact situation Debulking may be helpful both for aspergillus and zygomycetes, but in my own experience, it comes down to individual type cases. Some can be

operated on; some can be debulked; and some can't. And I don't think you're going to see any prospective, randomized study with surgery. It is something that every clinician has to look at at the bedside, and I would say in my own experiences, debulking of some of these things, if it can be done, is probably to the advantage of the patient.

Now, what about drug combinations? With aspergillus, there have been a series of case reports, in vitro stuff suggesting that amphotericin B in flucytosine might have some additive effects, amphotericin B and rifampin.

But I'm not convinced or have seen any clinical studies that would suggest that these compounds actually add to the final outcome of the patient, and some have toxicity and drug interactions which become problems in the kind of noisy type patients that we end up with today with aspergillus.

More important, I think, on the wards today has actually been the issue of polyenes and azoles together. There's always been a concern about this in an antagonism in animal models, particularly if the azole is given before the polyene.

But I'm going to say that in general down in the clinics and stuff like that, what we've

probably seen more often has been some type of additive effect or surely not antagonism or final outcome differences.

And I do that by looking at some of the data that we see in retrospect. Amphotericin B is commonly or lipid product is commonly given early, and then if patients are successfully managed or controlled, itraconazole is then given in sequence.

Well, if I go back to the Mycosis Study Group, and again, I hesitate to say this means anything because, again, these are not randomized situations, but if you look at the patients and look at the death rates of patients on amphotericin B by itself, the death rates are about 36 percent versus the amphotericin and itraconazole; the death rates were about eight percent.

Surely that does select out a patient population that has got and survived long enough to receive itraconazole, but it surely doesn't suggest in any way, shape or form that we're having antagonism here, and maybe, just maybe this additive effect is making some impact.

Studies need to be done to confirm these things. More data, animal models needs to be done. New drugs, old drugs, improved fungicidal activity,

but I believe the combination therapy is the wave of the future, and there is nothing in the data at this stage to say more drugs is harmful. If anything, maybe they're better.

Tom Patterson is in the audience. This is Tom's review in Medicine on a series of patients, a very, very large database, and I think if you break it down with amphotericin B by itself, itraconazole, and the combination you can see here, you can see some improvement in success rates with the combination compared to amphotericin B, but again, these are not randomized. These are selected patients that are put here, and I think the important point is he broke them up into severe versus less immune suppression, and as you're seeing multiple, multiple times, the underlying disease is a major harbinger.

So that, in fact, amphotericin B may work better with less immune suppressed patients. The combination may work better. Even itraconazole may work better.

And remember that when you're comparing these patients, they're not randomized. You and I know that probably itraconazole gets a better population of patients or a patient population that is not quite as sick as the amphotericin B containing

group.

But if you look at the whole big picture of things, even in this particular study coming back, the combination therapy surely has seemed to do okay. Whether it's better I can't say, but surely it has done okay.

I want to bring up combinations just quickly in vitro. I bring this up, an old study that I did a long, long time ago to emphasize combinations as important. This was cilofungin, and old beta glucan synthase inhibitator. We heard about one today. This was one of the older ones.

Nicomycin, a chitin synthase inhibitor. These are two cell wall, active antibiotics. This was aspergillus in kind of a titer controlled combination therapy here, and you can see the MICs are very high with the two drugs by themselves, but you start putting them together and you get dramatic synergistic activity.

And, again, there is a series of studies that have shown combination therapy can in some circumstances get in vitro synergy. Some circumstances in animal models, and again, I would say the emphasis, the emphasis in the future, I suspect, will be combination therapy, and even today when we

talk about caspofungin, we're really kind of talking about combination therapy because many of these patients still have polyene in their tissue when they receive this drug.

Now, the new agents, in the last seven minutes or so. I went through the series of other things and strategies for drug resistance in relationship to aspergillus, but I actually think the biggest impact besides strategies for prophylaxis is going to be new drugs.

How can they help? I think they can get better antifungal spectrum, reduce toxicity, less drug interactions, not unimportant in this patient population. These are noisy patients and on a lot of different drugs. And the fungicidal activity and eventually used in combination. Will they help? Yes, and I'm going to show you, I think, why.

They're almost new antifungal agents. The lipid products have now been around for four or five years. I think have been shown to be effective in the refractory case of aspergillus in the 40 or 45 percent range.

And I hate to put this up there because I'm sure somebody will knock it down, but it's perfect. It's the 40 percent rule. It seems like all

of these combinations that come through in intolerance and refractory patients, the successful rates, if they're successful at all, come in the range of about 40 percent.

The safety of nephrotoxicity matters as Wingard has shown in certain high risk populations. In our own situation, nephrotoxicity does matter. These are a lot of patients with a lot of organ problems, and simply we can't deal with nephrotoxicity. So many of the patients are on the lipid products because nephrotoxicity matters.

They're been used empirically very successfully. They are costly, and for our hospitals, they become very difficult issues in management of budgets.

The comparison of products has recently been done, and in the final analysis, at least with ABLC and AmBisome, as far as a final efficacy data, really it's hard to prove that any one of these products is better than the other.

And finally, recently itraconazole was approved. It has some efficacy data, but surely we would like to see more, particularly in the age of patients with reduced renal function.

I just brought down the amphotericin B

complex to give you some background tot his. This was a study by Walsh of about 560-some patients, and kind of the complete response and how it's broken down into complete and partial response and stable and, if we've got it over there, failures. You can add them up.

I bring up the issues here. As you can see, they are broken down into success rates, and I think as you get away from pulmonary and disseminate it to some of these other categories, the successful rates tend to be a little bit better.

So the site of infection may be a little bit better. This figure of about 42 percent or so is going to be pretty solid actually because Jeri Matera kindly, from the Liposome Company or Elon, I guess, today, gave me the most recent clear data last week on about 180 patients that they have followed prospectively sine licensure of ABLC in aspergillus.

And believe it or not, the success rates of both partial and complete is 39 percent, which is again the 40 percent rule invalidates this previous study.

Now, what about the new agents? There is the series here, the triazoles, posaconazole, ravuconazole, voriconazole that are coming in and are in studies as we talk; a series of azoles outside.

Today we're going to talk about caspofungin. There are a couple of other kind of candins or candins in the pipeline. There's a polyene liposomal nystatin, and a series of other compounds here.

Although recently the azasordarins didn't show quite as much activity against aspergillus as I would have liked, these are potential drugs either in combination for the future.

Well, what about the ones that are actually in studies? The best I can tell you up to date from ICAAC and what the success rates are. This is Nyotran, a liposomal nystatin that was at the 40th ICAAC, refractory and intolerant, very similar type patients that you're talking about today. The dosing toleration, infusion related toxicity events, nephrotoxicity events here, and response rates if you put it together was about 32 percent, of which I think there was one patient that had a complete response rate, and the survival rate, as you see here, is about 40 percent.

So that Nyotran as to polyene, and that's the most recent data that I have.

I'm not going to spend much time on this one because you'll hear much, much more about this and in more detail, but this was caspofungin, again, in

the refractory or intolerant polyenes.

And I'll just come down to this salvage therapy, favorable response of 41 percent, and the details of that will be elicited in the next couple of talks.

Posaconazole that was presented at the ICAAC meetings here, if we focus here, it's an oral preparation. If we focus here, it's an open, noncompetitive trial, 800 milligrams, invasive fungal infections are refractory. Standard therapy, and let's go down to aspergillus, 22 patients that I'm aware of right now with a complete response rate or partial response rate of about 50 percent; again, in that 40-50 percent range.

And finally, voriconazole. Again, this was also presented at actually the IDSA meetings, and I apologize for this slide in a way because I guess I'd never be a commercial type person. I just cut off the other 30 percent down here and just left it by. So actually the complete response rates start about 35 percent here on this axis and go up.

And I think there's an important issue here that needs to again be emphasized. In the success rates, in the complete and partial response, in an open trial, in an open trial of aspergillus for

intolerant or refractoried patients, of all patients the success rates run between 40 and 45 percent.

But then you break it down into hematology and non-hematology type patients, and this will drop down a little bit, around 37, 38 percent, and go very high, up to the 60, 65, 70 percent in non-hematological patients.

Again, the substrate, the protoplasm, the underlying disease is a major marker to the outcomes of these patients and has to always be figured into the final endpoints that are measured.

So in summary, and I've actually finished almost on my 30 minutes, the next five years. The single biggest advance for antifungal drug resistance, in my opinion, will actually be new drugs.

Like the drugs, the classes that we talk about today, tomorrow and next week, they will not cure every infection or prevent every infection as our immune compromised population increases. I would like to say that I think we should focus as much not only on treatment of these infections, but prevention of these infections, and we will make impacts.

But I do think they will make a positive clinical impact if properly studied. I have seen these drugs in action on clinics. I've seen the

opportunities to interact with these drugs both in combination or substitution, and the issue of the drug interactions and various things, and in the end, these will be the things that improves our survival rates and our ability to actually push the envelope in the underlying diseases that many of these patients have.

I'm going to finish with that.

ACTING CHAIRMAN GULICK: Thanks very much.

Are there one or two specific questions from the Committee members to Dr. Perfect?

Dr. Graybill.

DR. GRAYBILL: I have one. I'd like a little bit to disagree with your first thing. I think in the next five years the biggest advance will be early diagnosis, and you already said that in trying to prevent these infections.

Aspergillus, zygomycetes and fusarium are angio-invasive. They block our blood flow. They cause tissue infarction. An abstract at the ICAAC this year showed that you got much less amphotericin B into infarcted lung than you did into surrounding lung.

So I think there's only so much you can accomplish with whatever drug, and I think these drugs are very good. And the problem you may reach with

this 40 and 50 percent response rate may be that you're trying to deal with areas where the aspergillus just isn't reachable by the drug.

And another concern that I have is that I think our life is going to change a lot as voriconazole gets used prophylactically. I agree with you absolutely about your combination statements when the drugs are given together, but I have a little bit of concern when we're not going to start using the voliconazole first as empiric therapy and as prophylactic therapy based on Tom Walsh's study, and we'll have a lot of patients that are on voriconazole when the amphotericin may later be added, and that's exactly the situation in which this antagonism has been claimed.

I don't know how it's going to turn out, but I think there is a potential for a problem at least in that area.

And the last comment I'd like to make, which is one just to us a word to put together all of the things that you said about characteristics, is that when you have these small studies, there is tremendous selection bias not only in terms of who gets the amphotericin or the itraconazole, but in terms of how long they're treated before they get

turned over to the new drug.

On voriconazole, the people who got treated for just two weeks and got the new drug had the higher mortality than the ones who survived for four weeks and got the new drug. So there are so many things that affect the outcome here.

I think you summarized a lot of it very, very well, but it's really tough to figure out how these drugs are going to sit in this place.

Thank you.

DR. PERFECT: Dick, I agree. I couldn't say more. I put the diagnoses up there and the types of testing systems. I put it up there because I think we need to have more. I'm just not convinced that the immediacy of that is actually going to come up to actually drive therapy in the next year or two. I think they will be out there, but it's unclear whether and how well they will be used.

The other thing you're talking about, you're exactly right. That 40 percent rule is a combination of both where the disease process is, the burden of organisms, and the underlying disease.

And I don't know how much more we will make on that particular statistic, but as you mentioned, earlier, earlier types of issues of

treatment, prophylaxis, prevention are, I believe, the wave of the future to prevent these things.

And your concern, your concern about the issue of new triazole being used, something you're thinking down the line is a potential concern because there has been antagonism between the azoles and the polyenes in animal models, and there may be issues where a lot of azoles are used first rather second like many of the studies that we have today.

So I do share your concerns on that, but I think the focus of the future will be actually in prevention of these infections rather than actual treatment, and that's what I wanted to emphasize today.

Yes.

ACTING CHAIRMAN GULICK: Dr. Kumar.

DR. KUMAR: Dr. Perfect, thank you for your presentation, but I have a very specific question to ask about aspergillosis.

Although we have made very incremental improvements in the timepiece that we have, my question to you is: how best can we evaluate these different treatments for CNS aspergillosis?

And second, among clinicians right now, the lipid preparations are constant. There's sort of

a gut sense to just increase the dosing of lipid preparations to treat the CNS aspergillosis.

What are your comments regarding that, and what do you think are the best treatments for CNS aspergillosis?

DR. PERFECT: Okay. You asked a very specific question and a very specific disease process. Central nervous system aspergillosis, which prior if you look at the data in the literature has a very, very high mortality in some situations. Underlying disease in certain transplantations and stuff is probably up to 100 percent mortality.

She's asking how do you evaluate those things and what do you think about them today?

These are really complex issues, and a lot of times they will push the polyenes as high as they can to try to get brain penetration and control that.

There is complex issues on this because actually the management of these things may also entail surgery and the ability to debulk some of these things, not debride them, but debulk them, and I think that's an important issue.

My experience recently on these things, if you look at the data, you saw a couple of cases on the data that's being presented today that were

successfully managed. We're talking in the 25 percent range with that compound. I think with other compounds, we're still talk about a quarter being successfully managed.

These are complex issues. My own feeling on this is I've had some experience with other compounds, and I attend to the last patient I had. I can give you the last patient I had. We push voriconazole in very high amounts, and we were able to successfully control that infection in the central nervous system.

But like everything else in these patients, we still can't control the underlying disease, and that patient actually expired from the underlying disease.

These are individual type cases. There is a role potentially for surgery if you can do it. There is a role for some of these triazoles that do penetrate into the brain fairly well, and some of them that have worked very well in other non-aspergillus type of mold infections, and how you manage those become individual cases, and how you detail the evaluation of this.

Again, you're not going to have hundreds and hundreds of cases. So it's going to be somewhat

difficult to say this is the best regimen.

ACTING CHAIRMAN GULICK: Okay. Actually, I think we need to keep moving. I'd like to thank Dr. Perfect for setting the stage for the rest of the day.

Next will be the sponsor presentation from Merck Research Laboratories. Dr. Jeff Chodakewitz will make some opening comments.

DR. CHODAKEWITZ: Good morning. I'm Dr. Jeff Chodakewitz from Merck Research Laboratories, where I'm responsible for the infectious disease clinical research area.

I'd like to start off by thanking the members of the Advisory Committee and the FDA for the opportunity to present at today's session. We're very excited to be able to discuss results from our studies with caspofungin.

I'd like to make just a brief introductory comment or two before our formal presentation begins, and my goal would be to try to put some perspective on Merck's decision to accelerate our NDA submission of caspofungin, focusing an indication on the treatment of patients who are refractory to or intolerant of other therapies with aspergillus infection.

As you're heard from Dr. Perfect, while not common, aspergillus is noted with increasing

frequency in the highly immunocompromised population, and I think very consistent with his comments, that aspergillus remains a very difficult to treat infection, and unfortunately remains associated with high mortality.

Often these patients run out of therapeutic options, and I think you'll see that also as Dr. Sable discusses some of the patients who were enrolled in our salvage aspergillus study.

Thus, we believe, and I think it was reflected in Dr. Perfect's comments and others', that there is a very urgent need for new agents to treat invasive aspergillus, particularly drugs which work via new targets and are well tolerated.

We believe that caspofungin represents such an important therapeutic step, and it's really based on that belief that we've accelerated our filing, focusing on aspergillosis, while our other studies continue.

As you'll hear, caspofungin acts via novel mechanism of action, specifically inhibiting cell well synthesis in a number of clinically important pathogens. We believe that the rigorously documented clinical responses and the very favorable safety profile that will be presented, combined with the

urgent medical need, really emphasizes the value of having taken this strategic approach.

I'd like to now turn the program over to Dr. Tamara Goodrow from our regulatory affairs area, who will continue our presentation.

DR. GOODROW: Good morning, Mr. Chairman, members of the Advisory Committee, the FDA, ladies and gentlemen. My name is Dr. Tamara Goodrow. I'm from the Department of Regulatory Affairs at Merck Research Laboratories.

I am pleased to be here today to discuss Cancidas, Merck's trade name for caspofungin acetate. As Dr. Chodakewitz just mentioned, Cancidas is a member of a new therapeutic class of antifungal agents which by acting via a novel mechanism addresses a serious medical need for alternative treatments of invasive aspergillosis, as well as other fungal infections.

It was based on initial evidence of efficacy and safety, as well as the potential to fit an unmedical need for the treatment of invasive aspergillosis that Cancidas was granted fast track designation by the FDA in May of 1999. I would like to provide a few brief introductory remarks before Dr. Carole Sable presents her results of our development

program for Cancidas.

The presentation today will focus primarily on the data supporting our new drug application for the following indication. Cancidas is indicated for the treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies.

Although today's presentation will focus on the efficacy and safety data supporting the use of Cancidas for salvage treatment of invasive aspergillosis, this drug is currently being developed to treat other fungal infections. As you have seen in the Advisory Committee background package, some of the data obtained in studies in other fungal infections provide important supportive information for the development program for invasive aspergillosis.

This slide shows a summary of our ongoing development program for Cancidas. This program includes studies to support treatment of localized and invasive candida infections, as well as invasive aspergillosis.

In addition, studies in empiric therapy of patients with persistent fever and neutropenia and a pediatric program have recently been initiated. As you will hear in Dr. Sable's presentation, the Phase

II studies in documented localized candida infection provided initial clear evidence of antifungal activity in humans, and form the basis of our dose selection of our studies.

The Phase II and III studies in patients with candida infections also provided safety experience in patients treated with caspofungin in blinded comparator controlled trials.

In the presentation today, you will hear about the novel mechanism of action of caspofungin and its activity against both candida and aspergillosis species. You will hear that caspofungin exerts clear fungicidal activity against candida.

However, defining the in vitro effects of a new class of antifungal agents against aspergillus presents a challenge. Consistent with its novel mechanism of action, caspofungin has been shown to kill aspergillus cells with active cell wall synthesis.

Thus, caspofungin demonstrates clear in vitro activity, but does not fit the classic definition of fungicidal or fungistatic.

In the presentation today, Dr. Sable will also describe some interesting aspects of caspofungin's pharmacokinetic, metabolism, and

elimination properties.

The development program for Cancidas has many unique aspects. Due to the life threatening nature of invasive aspergillosis, the dose selection was performed in patients with candida infections.

In addition, a noncomparative study design was used to evaluate the efficacy and safety of caspofungin in invasive aspergillosis. Noncomparative study designs have been used for other approved therapies for the salvage treatment of aspergillosis in refractory or intolerant patients.

However, as Dr. Sable will describe later, several steps were taken to insure that the quality of the data from the study was very robust, including the use of strict definitions of disease and outcome, a requirement for documentation of disease and outcome, and review of all cases by an expert panel.

The strict application of the criteria in this study design has resulted in the evaluation of a small, but well characterized patient population with invasive aspergillosis.

In addition, as recommended by the FDA, an historical control study was conducted to further support the efficacy of Cancidas by allowing a comparison of the efficacy of caspofungin to that of

standard therapies.

And lastly, to provide additional supportive data and to allow for access of Cancidas for salvage treatment of invasive aspergillosis and serious candida infections, the development program included a compassionate use study which includes similar strict criteria for diagnosis and definition of outcome.

The results of each of these studies have consistently demonstrated efficacy of Cancidas against aspergillosis infections in patients with poor prognostic factors who are refractory to or intolerant of standard therapies. They also show that the safety profile of Cancidas is very favorable with few clinically relevant drug interactions. This drug is also generally safe and well tolerated.

As I mentioned earlier, this safety profile is based not only on the results obtained in the invasive aspergillosis noncomparative trial, but also in results obtained in large comparator controlled trials evaluating Cancidas for the treatment of candida infections.

In addition to our speakers, Merck has brought several consultants to the meeting today so that they are available to facilitate the Advisory

Committee's discussion and deliberations over a wide range of subjects, including drug metabolism, clinical pharmacology, mycology, and infectious disease. They are listed on this slide.

We have Dr. Richard Kim, Dr. Gary Koch, Dr. John Rex, Dr. Thomas Walsh, Dr. Thomas Patterson, Dr. Jack Uetrecht, and Dr. Frank Odds.

The outline for today's presentation is as follows. First, Dr. Sable will provide a background on our overall development program for caspofungin. She will then discuss the preclinical microbiology and clinical pharmacology of caspofungin, followed by the clinical efficacy and safety information that supports the use of caspofungin for the treatment of invasive aspergillosis.

Lastly, Dr. Chodakewitz will provide concluding remarks that will summarize how the information presented provides clear support for our proposed indication for the treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies.

I would like now to turn the podium over to Dr. Sable.

DR. SABLE: Good morning. I'm Dr. Carole Sable from the Clinical Research Department at Merck

Research Laboratories, and I appreciate the opportunity on behalf of Merck to present the results of the caspofungin development program.

As you've heard from Dr. Perfect this morning, invasive aspergillosis is an increasing problem in the immunocompromised host, and in fact, is the leading cause of infection related mortality in many transplant centers.

Mortality in patients with documented disease may exceed 90 percent. The only drug approved for first line therapy of patients with invasive aspergillosis is amphotericin B deoxycholate, which has limited efficacy and is associated with often significant toxicity.

In the past decade lipid formulations of amphotericin and itraconazole have been introduced and are associated with less toxicity, but there is still morbidity and mortality which remain exceedingly high, and there's a clear medical need for new therapeutic alternatives.

Caspofungin has been identified as an agent which may confer potential benefit in the treatment of these patients. It is a member of a new class of antifungals, the echinocandins which inhibit the synthesis of the fungal cell wall, a target which

is absent from mammalian cells.

The spectrum of activity, as we'll discuss this morning, includes aspergillus and candida species, and because of its unique mechanism of action, cross-resistance with azoles and polyenes is not expected.

Although these are potentially beneficial characteristics for the treatment of patients with invasive aspergillosis, they're also beneficial for the treatment of other documented fungal infections, and in fact, as Dr. Goodrow mentioned, the treatment of invasive aspergillosis is only one component of the overall development program for caspofungin.

The overall objective is to demonstrate safety, tolerability, and efficacy of caspofungin in well documented infections due to aspergillus or candida species, and to confirm that caspofungin is at least as effective as amphotericin B and fluconazole in the treatment of patients with candida infections in the setting of randomized comparator controlled trials.

In addition, to show that it has a favorable safety profile with few drug-related adverse experiences, including minimal, if any, nephrotoxicity and few significant drug interactions.

Because of favorable early results in treatment of patients with invasive aspergillosis, the aspergillus component of the program has been brought forward, and in this setting, the specific objective is to demonstrate efficacy in the treatment of patients with invasive aspergillosis who have limited therapeutic alternatives.

Because a randomized controlled study in this disease would be very difficult, data are obtained from a noncomparative study with additional contacts placed by data from the historical control.

We have attempted to implement rigorous criteria for documentation of disease and outcome, requiring documentation supporting those facts to make the data from the study as interpretable as possible.

And in addition, in these seriously ill patients who require longer courses of therapy to demonstrate a favorable safety profile with few drug related adverse experiences.

What I'd like to do now is to take a step back, review the data from the development program that led to the decision to bring forward the aspergillus component of the program.

In the Advisory Committee background, the extensive evaluation of caspofungin has been

summarized in more detail. What I'll do this morning is focus on the key findings in the following areas of the program: preclinical microbiology, clinical pharmacology, efficacy, and the safety profile.

I'd like to turn first to preclinical microbiology. Understanding the mechanism of action and spectrum of activity of caspofungin was instrumental in providing a foundation for development of the drug and the design of future clinical studies. We'll also focus in more detail on the activity of caspofungin against candida and aspergillosis species.

This schematic diagram shows the structure of the fungal cell wall and cell membrane and includes the transmembrane enzyme, beta-(1,3)glucan synthase.

As you've heard from both Dr. Chodakewitz and Dr. Goodrow, caspofungin inhibits the synthesis of Beta-(1,3)glucan in the fungal cell wall, which is important for the structural integrity of the cell wall of a number of pathogenic fungi, including aspergillus and candida species.

This novel mechanism is distinct from the available agents, the polyenes and azoles, which act against ergosterol on the cell membrane. As a result, because of the unique mechanism of action, cross-resistance of caspofungin with the azoles and polyenes

is not expected.

In addition, if we look at resistance to caspofungin itself, in laboratory experiments designed to generate resistant mutants, the development of resistance to caspofungin was a rare event, occurring at only one in ten to the eighth candida cells.

Caspofungin has been evaluated against a range of pathogenic fungi, and we have seen in vitro activity against aspergillus and candida species which has been confirmed in in vivo animal models.

In addition, in a panel of isolates with known intrinsic or acquired resistance to fluconazole, amphotericin B, or flucytosine, there was no cross-resistance with caspofungin.

Caspofungin does not have clinically useful activity either in vitro or in animal models as monotherapy for Cryptococcus neoformans.

Caspofungin has also been evaluated using in vitro susceptibility testing against a range of other filamentous and dimorphic fungi. Because standardized susceptibility methods for echinocandins are not defined and there are few validated animal models for these other pathogens, the clinical relevance of these in vitro findings is not yet certain.

Because caspofungin works by a unique mechanism of action, it's important to take a few minutes to review the information that we have against candida and aspergillus.

Against candida, broth dilution endpoints are 100 percent inhibition of growth across candida species. In in vitro kill curves, we see fungicidal activity with a two log reduction in colony forming units, which is consistent with results seen in sterilization of organs in animal models.

Caspofungin has been evaluated in a number of animal models of disseminated candidiasis to evaluate different types of immune suppression. What I'd like to do is to show you the results of the most stringent model that we've tested. The results across the studies have been consistent.

In this study, which is disseminated candidiasis in chronically pancytopenic mice, there were two endpoints used: survival and reduction in tissue burden. This slide displays on the Y axis percent survival, on the X axis days post infection.

In this model animals are inoculated on day zero. After a 24-hour delay, the animals are treated with dosing regimens as listed here daily for seven days.

In addition, on day minute three, immunosuppression with Cytoxan is initiated and continued just through dosing, as well as 21 days post dosing so that the animals remain immunosuppressed after dosing has been complete.

What we see in this white line is that all the sham treated controls are dead by approximately day 26. In contrast, both dosing regimens of caspofungin had survivals of approximately 80 percent or higher, which is similar to what we see with comparable doses of amphotericin B.

In contrast with fluconazole, there are fewer animals surviving, which is most notable at later time points in the experiment.

The second endpoint which was used was tissue burden, and what this slide displays are the same treatment regimens that had been displayed for survival on the last slide.

Looking at both log colony forming unit reduction, as well as the percent of kidneys which were sterilized, and this is at the endpoint of the study, which is day 28, what we can see is at both doses of caspofungin there were reductions in CFUs as well as animals which had sterile kidneys which were below the limit of detection for CFUs.

The results were similar to what was seen with amphotericin B. For fluconazole, there were fewer animals which were surviving to the 28 day endpoint, but you can see that there were smaller reduction in CFUs and fewer animals which had sterile kidneys.

In contrast to candida, it has been more difficult to characterize the activity of caspofungin against aspergillus. We see a clear in vitro effect, but the activity does not fit the classical definition of fungicidal of fungistatic.

Morphologic alterations of hyphae are seen with blunting and abnormal branching after exposure to caspofungin in vitro. Broth dilution testing shows a substantial inhibition of growth, but complete inhibition of growth is not routinely seen.

In addition, in looking at a quantitative analysis of activity, we did not see a consistent reduction in colony forming units. What I'd like to show you on this next slide is the reason for this, and the reason for this is not detection of colony forming units in filamentous organisms is not unique to caspofungin.

On the left we see with candida and other yeasts with single cell organisms that as you're

killing individual cells you actually see a direct reduction in colony forming units.

In contrast, with filamentous organisms, such as aspergillus, you may have a significant effect by killing a number of cells in the hyphae organism, but you may still get the same number of colony forming units when that is assessed as a measure.

If with cell wall active agents, such as caspofungin, you were causing increased fragility of the filamentous organisms. It is even possible that you may not see just not change, but potentially an increase in CFUs.

Because the accuracy of colony forming unit assessments for filamentous fungi is less certain, we have not used CFUs in our models of filamentous fungi, most notably for aspergillus.

We did feel it was important to evaluate in more detail exactly what the activity was of caspofungin against aspergillus, and what I'd like to tell you is the technique that we used and show you the results from these studies in comparison of caspofungin to amphotericin B and itraconazole.

What we used for vital dyes, which are able to differentiate viable from dead cells after exposure to drug, and we actually used two different

dyes. We have a viable stain, CFDA, which enters cells and is cleaved by an esterase. When that occurs, the cell fluoresces, present only in living cells. So viable cells fluoresce; dead cells do not.

The second die, which is DiBAC, enters into cells only when they're dead and fluoresce when they bind to phospholipids. So with this dye, fluorescence occurs only when the cells are dead and not when they're alive.

When we look at these types of dyes, what we see is that caspofungin kills cells where active cell wall synthesis occurs, at the tips and branch points of hyphae consistent with its mechanism of action.

What I'd like to show you in these next two slides are the results of these staining experiments, and they have eight panels across the top. You see phased microscopy, and on the bottom are the results with the vital dyes.

On the left is the untreated control. So with the viable stain, what you see is fluorescence across all of the filamentous strand.

With amphotericin B fungicidal agent, you do not see fluorescence. With itraconazole, which has been classically considered to be a fungistatic agent,

you see a large area fluorescence, and caspofungin is in between those two treated groups.

If we turn now to the nonviable stain, again, with the control on the left, we see that with untreated cells, there's no fluorescence. With amphotericin B, widespread fluorescence, and with itraconazole a little fluorescence, and you can see here with caspofungin many more areas of fluorescence. The areas of haze are actually tips of the hyphae which have the least theracytocella (phonetic) contents.

So these experiments show that the activity was consistent with the mechanism of action. We've also evaluated caspofungin against a range of animal models with disseminated aspergillosis, and in this study which is a murine model of disseminated aspergillosis in chronically pancytopenic mice with an endpoint of survival, and this slide is set up in the same way as the similar candida study with percent survival on the Y axis, days post infection on the X, treatment at day zero, a 24-hour delay, seven days' dosing, with immunosuppression beginning before inoculation and continued for a total of 28 days.

In this experiment approximately 20 percent of the sham treated controls were alive at day

28, and in contrast both doses of caspofungin were similar to amphotericin B with survival out to day 28 showing that there was sustained activity after dosing had been completed in a setting of continued immunosuppression.

So across all of the studies which have been performed to evaluate the preclinical microbiology of caspofungin, we have shown that the spectrum of activity includes Candida albicans, non-albicans candida species, and aspergillus.

Caspofungin is fungicidal for candida species. Caspofungin demonstrates clear activity against aspergillus. In vitro it kills cells with active cell was synthesis, effects which are consistent with its mechanism of action, and in vivo there's a sustained effect in severely immunosuppressed mice with disseminated aspergillosis.

Based on these findings, you can see why we were enthusiastic about the potential clinical benefit of caspofungin and went on to evaluate it in people.

What I'd like to do is to describe to you some of the key findings from our clinical pharmacology studies focusing primarily on an overview of the pharmacokinetics and metabolism,

pharmacokinetics in special populations, and evaluation of drug interactions.

Caspofungin has poor oral bioavailability in animals. It's actually less than .2 percent and is being developed as an IV formulation only. Once administered IV, the distribution, metabolism, and elimination profile are similar in the animal safety species and in man, and the plasma half-life in man is nine to 11 hours, which supports once daily dosing.

The plasma pharmacokinetics of caspofungin are controlled primarily by distribution into tissue. The tissue uptake is likely mediated through active transport. Although the plasma pharmacokinetics are controlled by distribution once the drug does get into tissues, we have also evaluated its metabolic fate. Caspofungin does not undergo oxidative metabolism. The metabolites are formed as a result of chemical degradation and hydrolysis.

Caspofungin is not a substrate nor an inhibitor for the cytochrome P-450 enzyme system. In an irradial (phonetic) label study designed to evaluate the elimination of caspofungin, a low level of covalent binding of caspofungin derived radioactivity to plasma proteins was seen.

We've also evaluated the pharmacokinetics

of caspofungin in a variety of special populations. In patients, caspofungin levels are similar to, but are more variable or range higher than seen in healthy subjects.

There are no clinically meaningful alterations in pharmacokinetics of caspofungin based on age, gender, or race. There's no significant alteration of pharmacokinetics in patients with renal insufficiency, and caspofungin is not hemadialyzed.

There is an increase in caspofungin AUC in patients with moderate hepatic insufficiency, and for these individuals a dose reduction is recommended.

We've also evaluated the potential for drug interactions with caspofungin in two ways. First, in formal phase 1 studies in which drugs which would be possibly administered with caspofungin or which represent specific metabolic pathways were administered and evaluated, and the second is in the setting of population pharmacokinetics in our clinical trials, which we screen for unanticipated drug interactions.

In the formal Phase I studies, there were no clinically significant interactions with amphotericin B, itraconazole or mycophenolate. In a Phase I study with caspofungin and tacrolimus, there

was a modest reduction in tacrolimus AUC of approximately 20 percent, with no change in caspofungin pharmacokinetics.

Because this reduction is modest, there's no need to change the dose in tacrolimus when caspofungin is initiated, and subsequent dosing should be managed through standard guidelines for monitoring tacrolimus levels.

We've also in Phase I studies evaluated the potential for interaction of cyclosporin A with caspofungin. In these studies, one or two doses of cyclosporin were administered with caspofungin to healthy subjects. Pharmacokinetically there was no change is cyclosporin pharmacokinetics, but there was an increase in caspofungin plasma levels of approximately 35 percent.

In addition, there were transient increases in ALT to two to three times the upper limit of normal in five of 12 subjects. Because this elevation occurred after one or two doses, interaction has not been evaluated further in healthy subjects, and cyclosporin had been excluded from the caspofungin clinical trials until recently when we had more clinical data to be able to insure that the risk-benefit of using the drug with caspofungin was

appropriate.

There has been one patients with invasive aspergillosis in a salvage study who was required to remain on cyclosporin and received both cyclosporin A and caspofungin for nine days. On daily monitoring of liver enzymes there were no elevations in liver enzymes seen.

Based on these data it's not clear whether the signal from Phase I is clinically significant, but we have elected to be conservative, and pending additional clinical data, the use of cyclosporin A with caspofungin is not recommended.

As I had mentioned, we've also used population pharmacokinetics to assess potential for drug interactions. In the patients in the caspofungin clinical trials who had underlying HIV infection, hematologic malignancies, bone marrow organ transplants, patients were receive a number of multiple, concomitant medications.

Alterations in caspofungin concentrations due to interactions are uncommon. Co-administration of inducers may result in reduced caspofungin concentrations and have been evaluated in more detail in formal Phase I studies.

So, in summary, the half-life of

caspofungin of nine to 11 hours supports once daily dosing. There was a low level of covalent binding to plasma proteins seen. Dose adjustments of caspofungin are not routinely necessary, but a dose reduction is recommended for patients who have moderate hepatic insufficiency.

There are few clinically significant drug, but the use of cyclosporin A is not recommended until additional data are available, and a caspofungin dose adjustment may be needed if co-administered with inducers.

The observations in the clinical pharmacology studies provided additional support for the potential benefit of caspofungin, and what I'd like to do is turn now to the data on the clinical efficacy and the studies in the development program.

I present first an overview of the entire development program, remembering that aspergillus is only one component of that program. Turn then to the rationale for dose selection, and then concentrate on data from the invasive aspergillosis study, with a brief summary of the efficacy from the Phase II candida studies.

As Dr. Goodrow showed, caspofungin is being evaluated in the treatment of patients with well

documented infections. The initial Phase II studies were done in patients with documented esophageal or oropharyngeal candidiasis. Dose ranging studies were conducted in these patients in blinded, comparator controlled trials. They also provide an important safety base.

Based on these data, doses were selected for broader evaluation. We've conducted a Phase III study in Candida esophagitis in which caspofungin was compared to fluconazole. Enrollment in the study is complete, and final safety data are available, and we'll present these later when we come to the safety information.

We have an ongoing study on invasive candidiasis in which caspofungin is being compared to amphotericin B, as well as the salvage aspergillus study which we'll discuss in great detail.

As preliminary data from these studies became available, studies in other populations were initiated. We've initiated a study in empirical therapy in febrile neutropenic patients. We've recently begun evaluation of pharmacokinetics in pediatric patients and have a compassionate use program in place for patients with candida aspergillus infections who are refractory to or intolerant of

other therapies.

What this translates to as far as clinical experience with caspofungin is that there have been over 600 individuals who have received caspofungin from one to 162 days. Approximately 350 have been patients. Most have received the recommended dosing regimen, which we'll come back to with dose selection, for at least seven days, including a smaller number who have received the recommended dosing regimen for a longer period, as well as patients who have received 70 milligrams for at least seven days.

In addition, there have been 274 healthy subjects of whom 126 have received the dosing regimen of 50 milligrams daily for at least seven days.

In addition, an additional approximately 100 patients have been on caspofungin in the ongoing blinded studies of invasive candidiasis or empirical therapy, and data on serious adverse experiences are available for those patients.

Typical dose ranging studies for invasive aspergillosis are not feasible because of the high mortality. Instead the selection of dose was based on an integration of data from preclinical microbiology, clinical pharmacology, and dose ranging studies in patients with candida infections.

So in summary, the in vitro susceptibility data demonstrated that the MIC-90 for aspergillosis in candida species was generally less than one microgram per mL. Because a specific PKPD relationship was not known for caspofungin or echinocandins, we selected a conservative target to maintain a plasma concentration above of at least one microgram per mL throughout the 24-hour dosing interval.

Multiple doses of 50 milligrams of caspofungin resulted in C-24 hours or troughs of at least one microgram per mL in 95 percent of patients. So the 50 milligram daily dose should meet the target plasma concentration.

What we also saw was that the mean trough concentration after 50 milligrams in the first few days of therapy was often less than one microgram per mL. In addition, a 70 milligram loading dose on day one produced levels above our target throughout therapy.

In the initial Phase II clinical studies of patients with Candida esophagitis, doses of caspofungin of 35, 50, and 70 milligrams once daily were evaluated. All three doses were effective and generally well tolerated.

We did see that the response at 35

milligrams was numerically lower than at 50 or 70 milligrams, and this was consistent with the population pharmacokinetics from the same studies in which lower trough concentrations were more commonly associated with an unfavorable outcome.

Based on the integration of these data, the dosing regimen that was selected for the treatment of patients was 50 milligrams daily, and for patients with serious of life threatening infections in whom low concentrations early in therapy may be a critical determinant of outcome, a 70 milligram dose on day one was put in place, and this is true for patients with invasive candidiasis or aspergillus.

What I'd like to do now is to turn to the data from caspofungin in the treatment of invasive aspergillosis. The primary study evaluating caspofungin has been in our salvage aspergillus protocol, Protocol 19.

There were 58 patients originally involved and submitted in the application with efficacy data based on expert panel assessments.

Subsequently, 11 additional patients have been reviewed by the expert panel. The results are consistent in the two groups, but I will present first the data on the original 58, and then come back and

provide a brief summary of the data from the additional 11.

In addition, in the compassionate use study, which used the same definitions for diagnosis and outcome, but where more limited data were collected at sites where the salvage study was not being performed, we have three patients with invasive aspergillosis.

As we had initial clinical data that showed some clinically promising results in caspofungin, we in discussions with the agency set up a historical control study to try to provide some additional context for the data which we've obtained on caspofungin in the noncomparative trial.

The caspofungin salvage aspergillus study is a multi-center, open label, noncomparative study with the dosing regimen as we've discussed. The diagnostic criteria for this study required documented invasive aspergillosis, and patients were required to meet criteria as being either refractory to or intolerant of standard therapy.

In this study, a favorable response was defined as a complete or partial response, and an unfavorable response included patients who were failures, as well as those who had stable,

nonprogressive disease.

All of the cases in the study were reviewed by an independent expert panel.

In our efficacy analysis, a primary analysis for efficacy was at the end of caspofungin therapy and included all patients who met the diagnostic criteria and received as little as one dose of caspofungin therapy and had any data on which to base an assessment of outcome.

In addition, because in many studies outcomes are presented in some patients who have received at least some minimal course of therapy because it's not likely in this disease that outcomes in the first few days to week of therapy would be likely to be very related to the therapy they received, we've performed a secondary analysis using the patients in the same criteria who then were treated for more than seven days.

We've also looked at an evaluation of relapse at four weeks follow-up visit and all of the patients who had a favorable response at the end of caspofungin therapy.

Patients in this study were allowed to receive secondary suppressive therapy with oral itraconazole if they were felt to be at continued risk

by their physicians.

Before I turn to the results from this study, we certainly recognize that there are challenges with noncomparator studies, and I'd like to review with you some of the key areas that we identified as having a potentially significant impact on the outcome of the study and what interventions we put in place in the caspofungin study to try to address these.

The areas that we identified were diagnostic certainty, the contribution of prior and/or concomitant antifungal therapy, documentation of response, and a consistent interpretation of definitions.

The diagnostic criteria for the caspofungin study were modeled after the Mycoses Study Group criteria. A definite diagnosis required histopathology or culture from an invasive procedure, and all patients with extrapulonary disease were required to have a definite diagnosis.

A probable diagnosis was, therefore, only applicable for patients who had pulmonary disease and required appropriate clinical and radiographic findings, plus positive cultures from bronco-alveolar lavage, sputum, or repeatedly positive galactomannan

ELIAS or PCR. And, again, probable is allowed only for pulmonary disease.

The definitions of refractory or intolerant to standard therapy are similar to those that have been used in other salvage aspergillus studies. Refractory was progression of disease or failure to improve after at least seven days of therapy with an amphotericin B formulation or itraconazole, and intolerant was doubling of serum creatinine or a serum creatinine of at least 2.5 milligrams per deciliter or other significant drug related toxicity.

In this study we required documentation to support the classification of patients as either refractory or intolerant.

Next, if we turn to the contribution of prior and/or concomitant antifungal therapy, the extent of disease was documented both at the initial diagnosis of invasive aspergillosis and at study entry. In refractory patients, this information was used to determine if the patients truly had progression of disease or if they had failed to respond to initial therapy.

In intolerance patients, it was used to verify the status of their infection at the time of

enrollment into the protocol. Concomitant antifungal therapy during caspofungin was prohibited.

And, finally, the doses and durations of all antifungal therapy for this episode of invasive aspergillosis were collected and documented.

We turn now to documentation of response. Seroassessments of signs, symptoms, and radiographic abnormalities were performed throughout the study. Favorable responses were defined as complete or partial response, and stable disease was considered unfavorable.

We collected reports and actual radiographs from all patients. Clear evidence of radiographic improvement was required for a patient to be considered a partial response, and a complete response required complete resolution of all attributable signs, symptoms, and radiographic findings.

In addition, recognizing that changes in immunosuppression may be significant determinants of outcome, we collected information on changes in immunosuppression, not only the patient's status at the entry into the study, but also throughout the course of caspofungin therapy, and we'll come back to this later as we discuss the results.

Finally, consistent interpretation of definitions. We empaneled a group of three international experts in invasive aspergillosis, including Drs. Thomas Walsh, Dr. David Denning, and Dr. Thomas Patterson. In our review, each expert assessed the diagnosis, the response to standard therapy, and outcome after caspofungin therapy for every case.

And their evaluation was based on case report form summaries, official reports of radiographs, procedures, histopathologies, and autopsies, as well as actual radiographic films.

If any of the experts disagreed with the investigator's assessment or requested additional information, the cases were discussed at a face-to-face meeting. At that point, a majority vote was considered final, and in fact, the experts were unanimous among themselves in all of the assessments of diagnosis and all but one assessment of outcome.

So, in summary, recognizing the challenges for noncomparative studies, in the caspofungin study we required strict criteria for diagnosis and outcome and documentation to support those determinations. We prohibited concomitant antifungal therapy and used source data, not only reports, but radiographs and had

every case assessed by an independent expert panel.

The assessments of the panel are primary and are the results we'll discuss here today.

We've talked now about what we've implemented in the study, and I'd like to turn now to the results from the original 58 patients enrolled. What I want to point out is that this in the subsequent slides will say 54. Of the 58 patients enrolled, 54 patients met the diagnostic criteria and had any information on which to base an assessment of outcome. These are the patients included in the efficacy analysis and are the patients which we'll describe.

As Dr. Perfect mentioned this morning, there are a number of factors which are known to be associated with either a better or worse prognosis with invasive aspergillosis, and as I describe the characteristics of the patients to you, it will be not only demographics, but also how the patients in the caspofungin study fit into some of those other prognostic criteria, and we'll come back to that when we discuss the actual outcomes in the study.

The patients in the caspofungin study were all adults. As expected, most patients had pulmonary disease, but the most common extrapulmonary diagnosis

was disseminated disease defined in our study as two or more noncontiguous sites or positive blood cultures. So pulmonary and sinus does not fit disseminated.

In addition, 80 percent of the patients had been refractory to prior therapy. The remaining 20 percent were determined to be intolerant. Seventy percent of the patients had a definite diagnosis, including all of the cases of extrapulmonary disease.

The patients also had significant underlying immunosuppression. Twenty percent of the patients were neutropenic at baseline, and approximately 70 percent had either hematologic malignancies or had undergone an allogeneic bone marrow or peripheral stem cell transplant.

In these patients with well documented disease and high prevalence of poor prognostic factors, the expert panel determined that 41 percent of patients had a favorable response at the end of caspofungin therapy, and if we look at patients who had only received more than seven days of therapy, the response rate is 49 percent.

These results are even more impressive if we walk through the kinds of patients and the responses that had been seen.

First, let's look at responses by site of infection. As expected, patients with pulmonary disease had a better outcome, but there were patients with disseminated infection who had a favorable response.

As expected, patients who were not neutropenic or had received low dose or no corticosteroids had a better outcome, but patients who were neutropenic, as well as those who received higher doses of corticosteroids also had favorable outcomes.

One of the other important factors is the patient's response to initial therapy, with patients who have been refractory expected to have a worse prognosis. In this study 81 percent of patients were refractory to standard therapy, and most of those patients had progression on that initial therapy.

There were also a smaller number of intolerant patients, most of whom, as you would expect, had nephrotoxicity. And I do want to point out that there were some patients who were considered to be both refractory and intolerant by the expert panel. They're classified in the refractory category because it was felt that that would be a stronger determinant of outcome.

If we look at responses by category, we

see that the overall response is not being driven simply by patients who are intolerant, but that patients who are refractory, including a large number who have progressive disease, had a favorable response rate of 34 percent.

Both of these groups provide important information, and it's necessary to really look in more detail both at the duration of prior therapy, as well as the type of therapies that these patients received. And I'd like to do that first with refractory patients and then for those who were intolerant.

In this study, 70 percent of patients had received more than 14 days of therapy prior to being declared refractory by their physicians, and of those who received shorter courses of therapy, 12 of the 13 actually had progression of disease.

The types of prior therapy, approximately one-third were refractory to more than one antifungal agent. In the patients who were listed as refractory to itraconazole were often also intolerant to an amphotericin formulation, a group who there are really limited therapeutic alternatives.

If we look at outcomes by prior treatment, you can see that there are favorable responses in all groups, including in patients who had been refractory

to multiple agents.

In contrast, patients who had been intolerant to other therapy received much shorter courses of antifungal treatment. Eight of the ten received fewer than 14 days of prior treatment, and the two patients who received longer courses were both intolerant to more than one antifungal.

Although it wasn't required by the protocol, eight of the ten had no improvement on that initial therapy, and the two who had some clinical improvement still had extensive disease. So we believe a group that you can actually assess the contribution of caspofungin to their overall outcome.

And if we look now at the outcome by treatment, you can see that responses were seen in patients who had been intolerant to either amphotericin B or lipid formulations of amphotericin.

We focused primarily to this point on baseline characteristics. As I mentioned, we also collected information on changes in immunosuppression through the course of caspofungin therapy, and we have seen favorable responses in patients who were not only receiving high dose corticosteroids at baseline, but who continued to receive corticosteroids throughout therapy.

In addition, favorable responses were seen in patients who were receiving other immunosuppressants, including tacrolimus with or without micophenolate.

We've also seen favorable responses in patients who had progression of their underlying disease on caspofungin therapy and patients who have received chemotherapy.

Finally, the responses that were seen the patients who were neutropenic did occur in patients who had eventual recovery of their neutrophil count prior to the end of caspofungin therapy, but evidence of clinical response was seen before recovery of their neutrophil count.

We focused up to this point on favorable response, which I had mentioned earlier included patients who had either a complete or partial response. What I'd like to do now is to point what we saw as far as complete or partial response in this study.

Reminding you of the very strict definitions that we used, which was that a complete response required complete resolution of all attributable signs, symptoms, and radiographic findings, and for a patient to be classified as a

partial response, they were required to have clinically significant improvement in radiographic findings.

And our expert panel interpreted our strict definitions very strictly.

At the end of caspofungin therapy, as we've discussed, a favorable response was seen in 22 patients. Three patients were considered to have a complete response, and 19 patients to have a partial response.

What I'd like to do is to show you an example of one of the cases that was considered by the expert panel to have a partial response as an illustration. This patient is a 67 year old male who had acute myelogenous leukemia. He had probably pulmonary aspergillosis and was initially treated with Abelcet.

He was treated with caspofungin for 34 days. On therapy, he was found to be in blast crisis and requested discontinuation of all treatment and discharged to home.

At the end of therapy, he was assessed as having a partial response.

This CT scan demonstrates the fact that the patient has an anterior infiltrate, as well as

this nodular lesion. The patient does have bilateral pleural effusions.

This is a different cut, also pre-study, but you can see the dense infiltrate as well as abnormalities on the right side.

These next two are CT cuts at the same levels at day 31 of therapy. You can see resolution of this area, smaller infiltrate, and this is the lower level where you can see the dense infiltrate. This is what's remaining, and this is one of the patients that was considered a partial response by the expert panel.

As I mentioned, we also evaluate relapse at a point four weeks after the end of therapy in all of the patients who had a favorable response at the end of caspofungin treatment. Seventeen of the 22 patients were evaluated at four-week follow-up. Two patients had died from their underlying disease in the interim, and three patients were lost to follow-up. Of those, two had been discharged to Hospice because of progression of their underlying disease, and one patient returned to their home in another state for additional therapy for their underlying malignancy.

Only one of the 17 patients who was seen at the four-week follow-up had a relapse of invasive

aspergillosis.

So in summary, there's been a high prevalence of poor prognostic factors in the patients involved in the caspofungin study. Eighty percent of patients were refractory to standard therapy, and 70 percent had received at least 14 days of treatment before being declared refractory.

Sixty-seven percent of patient had hematologic malignancies or allogeneic stem cell transplants. Seventy percent of cases had definite diagnoses, including all extrapulmonary cases, and most of the extrapulmonary cases were, in fact, disseminated disease.

In these patients, the expert panel determined that 41 percent of patients had a complete or partial response at the end of caspofungin therapy. Favorable outcomes were seen in high risk groups, including those who were refractory, had hematologic malignancies or bone marrow transplants, had disseminated disease, were receiving corticosteroids, or when neutropenic, and documented relapse was uncommon at a four-week follow-up.

The focus to this point has been on the original 58 patients involved. Now, as I mentioned, we also have data on 11 additional patients in the

caspofungin study, as well as three patients from compassionate use, and what I'd like to do is to provide a brief summary of the data in those two groups.

In the 11 additional patients, as assessed by the expert panel, the baseline characteristics were similar to the original 58. Nine of the 11 met diagnostic criteria, including six with pulmonary disease and three with disseminated disease. All nine were refractory to an amphotericin formulation, and favorable responses were seen in four of these nine patients, including three with pulmonary disease and one with disseminated disease.

In the compassionate use study, these three cases were evaluated by the same expert panel. Two of the patients had definite pulmonary, and one had disseminated disease, with the therapy to which they were refractory and intolerant listed here, and the expert panel determined that two of these three patients also had a favorable response.

So across the data that's available in caspofungin, we see a consistent response rate of approximately 41 percent in the original 54, when the data from the nine additional patients or the three patients in compassionate use are added.

As I mentioned earlier, we also conducted an historical control study to provide some context for the stat that we've obtained in the caspofungin study. We recognize that there are also challenges for historical control studies, and I'd like to point out a few of the areas where you could have potential bias or confounding and briefly address here, but as we discuss the study design, to tell you some of the things that we did in our historical control study in an attempt to address these.

One of the most important characteristics is identification of appropriate patients for comparison, which would be how the patients are identified, as well as the sites from which they are selected.

We've addressed this in the study design, and I'll come back to it, but we certainly recognize that despite our efforts, you cannot duplicate a randomized controlled trial by using historical control.

A second potential for bias is differences in diagnosis and management over time, and as we discussed the study to see how we tried to make the patients temporally similar in the historical control study to those in the caspofungin study.

Another source is information available in a retrospective review. Both the type of information and the completeness will not be the same as in a prospective controlled trial.

The objective of the historical control study, which was a retrospective medical chart review, was to describe the efficacy of standard antifungal therapy in patients with invasive aspergillosis and to serve as an approximate comparator group for the caspofungin aspergillus study.

Patients for this study were selected through a systematic identification of patients with invasive aspergillosis, treated with standard therapy at ten centers. Four of the ten centers also participated in the caspofungin study and enrolled approximately 50 percent of the patients in each study.

Patients were identified through a range of methods, including review of medical records, microbiology, pathology records, backward in time from December of '98 to January of 1995. This was intended to yield a consecutive series of cases at each site. The caspofungin patients were enrolled in the years 1998 and '99, and there was not overlap in enrollment in the two studies at the sites which participated in

both.

Potential cases identified through these mechanisms were screened for eligibility. Evaluation of outcome was performed by site investigators using the same definitions of response as were in the caspofungin aspergillus study.

This slide lists some of the key inclusion criteria that we tried to mirror in the historical control to match that of the caspofungin study. Patients were required to have definite aspergillosis from any site or probable pulmonary aspergillosis and to be adults.

One thing that could not be accounted for was the fact that in the caspofungin study, patients were receiving salvage therapy. They were either refractory or intolerant to standard treatment.

In the historical control study, patients were receiving primary therapy.

One thing which we did was required patients to receive at least seven days of standard therapy. This is the duration of time which they would have had to receive as a minimum before being eligible to enroll in the caspofungin study.

What this was designed to do was to eliminate patients who died early during standard

treatment, who would not have survived long enough to be eligible for enrollment in the caspofungin study.

There are, of course, other inclusion criteria in the prospective study, primarily safety criteria, which were not matched in the historical control study. We selected the characteristics, the criteria which we felt were most important for determining patients and being able to assess efficacy.

As I mentioned, the historical control study was primary therapy. We attempted to define subpopulations based on minimum entry criteria for the caspofungin aspergillosis study.

As we've discussed, the definitions of refractory and intolerant in the caspofungin study are listed here. Because the patients were receiving primary therapy, we defined as refractory in the historical control not improved at week one. In fact, most of these patients would not have been considered refractory to standard therapy by the physicians caring for them. So this is a very conservative definition.

For intolerant, patients were required to have both an elevated creatinine and to be improved at week one, and this is in contrast to what we saw in

the caspofungin study were most of the patients had, in fact, not been clinical improved.

From all of the cases which were potential cases that were screened, 229 make up the historical cohort which were abstracted. From these, it was prospectively defined that patients who were not refractory or not intolerant would be excluded from further consideration because they would not have been eligible for enrollment in the caspofungin study.

The remaining 214 make up the refractory or intolerant population.

The parallel the convention used by the expert panel in the caspofungin study, patients who had an indeterminant outcome at the end of therapy were excluded, and the remaining 206 patients are those which make up the primary comparison population.

As we've discussed the baseline characteristics in the caspofungin study, it's important to look at the types of patients that were identified in the historical control and their comparison to those enrolled in the caspofungin study, and what we can see is the populations are very well balanced. Underlying diseases are similar. The proportion of patients with neutropenia is not significantly different. The sites of infection are

similar, with again approximately 70 percent of patients in each study having pulmonary disease and disseminated disease being the most common extrapulmonary type of infection.

If we look at outcomes in the two populations, as we've discussed, there's 41 percent in the caspofungin study, and in the patients in this historical control study, 17 percent of patients who receive standard therapy had a favorable outcome.

We also looked at outcomes by the subpopulations that we had defined. You can see refractory. The number of intolerant patients is very small in both groups, but the results are similar.

If we turn now to look at outcomes by underlying factors, we can see that the favorable responses are higher in the caspofungin group across subgroups, although we do see that where you would expect there to be more unfavorable outcomes, such as with disseminated disease, the two groups actually do travel in parallel, but there is still a favorable benefit of caspofungin over standard therapy in each of these subanalyses.

And, again, the same is true of patients with neutropenia at baseline and those who were receiving corticosteroids with more favorable

responses being seen in caspofungin than in the historical control.

In addition to looking at a descriptive tabular display comparison of the two groups, we also made a more formal quantitative comparison in which we compared the likelihood of a favorable outcome in caspofungin in the salvage study to the likelihood of a favorable outcome with standard therapy in the historical control.

This procedure adjusts for potential imbalance in important baseline characteristics between the populations. And the protocol specified analytic method allows for adjustment from multiple baseline prognostic factors in the same patient, something which you can't get by just looking at tabular displays.

In this procedure, the following potential predictors of outcome were evaluated for strength of association to outcome in the historical control study. The four factors listed in the left in yellow are those which were found to be the strongest independent predictors of outcome in the historical control study. These were used to create a logistic regression model to address the presence of those characteristics in the populations.

This slide shows odds ratios down at the bottom with unadjusted and different models. An odds ratio of one would say that there's no association of treatment to outcome. If we focus on the unadjusted, we can see that there's an odds ratio of approximately three, which would mean the odds of a favorable to unfavorable outcome in caspofungin was three times that to seen in standard therapy, and the 95 percent confidence interval does not cross one, results favoring caspofungin.

You can see that with each of the different models constructed using different combinations of the predictors of outcome that the results were consistent.

What we can see from the comparison of the caspofungin study to the historical control study is that the patient characteristics and important risk factors were well balanced between the two studies. Caspofungin was more commonly associated with favorable outcomes than standard therapy in the historical control study. There was a consistent effect across subgroups and a consistent effect in both adjusted and unadjusted analyses, and the results support the efficacy of caspofungin in the treatment of invasive aspergillosis.

If we turn now briefly to candida, as we've mentioned, this is part of an overall development program, and because caspofungin is a member of a new class which works by a new mechanism of action, of efficacy in another documented infection provides additional support for the overall efficacy of the drug in the treatment of documented infections.

What I'd like to do is to briefly review the design of results from the Phase II estimation studies in oropharyngeal and esophageal candidiasis. There were two studies, Protocols 3 and 4, which both enrolled patients with candida esophagitis. Patients with oropharyngeal candidiasis were also included in Protocol 4 with the various dosing regimens listed here in comparison to amphotericin B.

In these studies, patients were required to have both symptoms and microbiological documentation of infection at study entry. A favorable response required both resolution of symptoms and a significant reduction in endoscopic or oropharyngeal lesions.

If we look at the percentage of patients with a favorable response at the test of cure, including all patients who met the diagnostic criteria and received as little as one dose of caspofungin, we

can see that all three doses of caspofungin were effective in a period at least as effective as amphotericin B in these Phase II studies.

We've spoken so far about efficacy in two distinct fungal infections. As Dr. Perfect mentioned earlier, a benefit of new agent in the treatment of invasive aspergillosis would also have a favorable safety profile, and we believe that caspofungin also offers this benefit, and I'd like to review the safety for you from both the preclinical and clinical studies.

As I've mentioned, the distribution, metabolism, and excretion of caspofungin in animal safety species is similar to that seen in humans. Caspofungin was evaluated in a number of studies, including at doses which produced exposures above that seen in humans, and across studies and species, caspofungin had a very favorable preclinical safety profiles.

The findings in the five to 27-week studies, which occurred at different doses, included mild elevations in serum transaminases in the monkey, histamine release in the rat, and irritation at the injection site in the rat and the monkey, and as we discussed the clinical safety, you see that we pay